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# Cicerone: stereotactic neurophysiological recording and deep brain stimulation electrode placement software system

**S. Miocinovic**[1,2], **A. M. Noecker**[1], **C. B. Maks**[1], **C. R. Butson**[1], and **C. C. McIntyre**[1,2]

[1] Department of Biomedical Engineering, Cleveland Clinic Foundation, Cleveland, OH, USA
[2] Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH, USA

## Summary

Stereotactic neurosurgery and neurophysiological microelectrode recordings in both humans and monkeys are typically done with conventional 2D atlases and paper records of the stereotactic coordinates. This approach is prone to error because the brain size, shape, and location of subcortical structures can vary between subjects. Furthermore, paper record keeping is inefficient and limits opportunities for data visualization. To address these limitations, we developed a software tool (Cicerone) that enables interactive 3D visualization of co-registered magnetic resonance images (MRI), computed tomography (CT) scans, 3D brain atlases, neurophysiological microelectrode recording (MER) data, and deep brain stimulation (DBS) electrode(s) with the volume of tissue activated (VTA) as a function of the stimulation parameters. The software can be used in pre-operative planning to help select the optimal position on the skull for burr hole (in humans) or chamber (in monkeys) placement to maximize the likelihood of complete microelectrode and DBS coverage of the intended anatomical target. Intra-operatively, Cicerone allows entry of the stereotactic microdrive coordinates and MER data, enabling real-time interactive visualization of the electrode location in 3D relative to the surrounding neuroanatomy and neurophysiology. In addition, the software enables prediction of the VTA generated by DBS for a range of electrode trajectories and tip locations. In turn, the neurosurgeon can use the combination of anatomical (MRI/CT/3D brain atlas), neurophysiological (MER), and electrical (DBS VTA) data to optimize the placement of the DBS electrode prior to permanent implantation.

*Keywords:* Neuromodulation; movement disorders; Parkinson's disease; neurostimulation; electrical stimulation; electrode; stereotactic neurosurgery; surgical planning.

## Stereotactic neurosurgery and deep brain stimulation

Stereotactic neurosurgery has been used in research for over one hundred years and it has gained acceptance into clinical practice since the 1950s [15]. The precision of target localization using stereotactic frames has improved since the inception of image-guided (MRI and CT) methods based on internal landmarks [17, 22, 27]. However, even with the increased accuracy of image-guided stereotactic targeting, it is often necessary to use neurophysiological microelectrode recordings (MER), and electrical stimulation to confirm and further explore the target [12, 13, 18, 26, 30]. In turn, stereotactic neurosurgical procedures typically require the integration of anatomical, neurophysiological, and electrical data to enable the neurosurgeon to make the most informed decisions possible.

Stereotactic neurosurgery is particularly relevant to deep brain stimulation (DBS). Over the last two decades DBS has evolved from a highly experimental technique to a well established therapy for a range of medically refractory neurological disorders [2]. To date, the most effective application of DBS technology is for the treatment of movement disorders. Surgical interventions for movement disorders have a long history, beginning with early studies that used lesions to eliminate activity in localized brain regions. Surgeons using stimulating/recording electrodes for target confirmation during ablative surgery found that high-frequency stimulation ($\sim$100 Hz) of the brain had behavioral outcomes similar to lesioning [3]. This realization transformed the world of functional neurosurgery, and DBS has become the surgical intervention of choice for Parkinson's disease (PD), essential tremor, and dystonia. In addition, DBS shows promise in the treatment of other neurological disorders such as epilepsy, obsessive-compulsive disorder, Tourette's syndrome, and depression. Currently the most common DBS procedures are for PD and they depend on precise localization and electrode insertion into the globus pallidus internus (GPi) or subthalamic nucleus (STN), small structures deep within the basal ganglia.

In current clinical practice, MRI-based surgical navigation systems are used in concert with stereotactic frame systems to target the nucleus of interest and select the initial electrode trajectory for DBS surgeries [7–10, 16, 21, 28, 29]. The anatomical target is identified by direct visualization of the nucleus in the MRI and/or a brain atlas co-registered with the MRI [24]. The stereotactic coordinates of the anatomical target are calculated relative to the fiducial markers of the stereotactic frame present in the image. In turn, the mechanical adjustments of the frame system can be calibrated to enable a surgical trajectory that follows the desired path [26]. Many believe that accurate placement of DBS electrodes for a maximal therapeutic outcome requires neurophysiological definition of the anatomical borders of the nucleus and identification of areas where stimulation causes side effects [23, 25]. Therefore, the target area is commonly explored with several microelectrode penetrations during which extracellular unit recording and microstimulation data are collected.

The final DBS electrode placement is selected after a review of the gathered anatomical and neurophysiological data. This crucial decision is often based on paper records which are inefficient and limit opportunities for data visualization. Traditional 2D brain atlases are typically used to estimate electrode position with respect to the anatomy by superimposing the atlas over plots of the microelectrode recording data. However, these atlas slices are not customized to each patient and they are often spaced at large and irregular intervals, so the closest available slice may not accurately capture the neuroanatomy of the given electrode trajectory. This is especially true when the surgical trajectory is at an oblique angle relative to the sagittal and coronal planes used in 2D brain atlases. More importantly, the fundamental purpose of DBS is to modulate neural activity with applied electric fields, but current neurosurgical navigation systems do not allow for visualization of the spread of stimulation.

To address these limitations, we developed the Cicerone software system for stereotactic neurosurgical planning, neurophysiological data collection, and deep brain stimulation visualization. This research tool integrates the vast array of data used in the implantation of DBS electrodes, with the goal of improving the therapeutic outcome of the surgery. Cicerone provides interactive 3D visualization of co-registered MRI/CT images, subject-specific 3D anatomical brain atlas, and neurophysiological data from microelectrode recordings. Furthermore, it displays predictions of the volumes of tissue that would be activated by DBS for any given electrode position and orientation in the brain. Cicerone can be used to define a pre-operative target location and trajectory for the DBS electrode placement and help select the location on the skull for burr hole (in humans) or chamber (in monkeys) placement. Intra-operatively, Cicerone allows entry of the microdrive coordinates and MER data, enabling real-time interactive visualization of the electrode location in 3D relative to the surrounding anatomy. In addition, the user can simultaneously visualize the DBS electrode and its predicted stimulating effects in relation to the neuroanatomy and neurophysiology. In turn, stereotactic placement of the DBS electrode can be optimized prior to permanent implantation with the combination of anatomical, neurophysiological, and electrical data.

Cicerone was developed to integrate the various data sets used in our scientific analysis of human and monkey DBS research studies. The human and monkey versions of Cicerone are conceptually similar, but due to differences in the surgical procedures they have been developed as two separate software applications. Both systems were written using VTK (Visualization Toolkit; Kitware, Clifton Park, NY) and Tcl/Tk (Tool Command Language; http://tcl.sourceforge.net) making them portable across platforms, including Windows. Version 1.0 of Cicerone is self-contained on a single CD, and auto-installs on a PC similar to any traditional Windows software. Cicerone is currently a research tool and not commercially available or intended for clinical use outside of IRB approved studies. Individuals interested in using Cicerone in their own research are encouraged to contact CCM.

## Human Cicerone

The Cicerone system was developed to address three issues. First, improve the intra-operative management of MER data. Second, provide the neurosurgeon with the ability to interactively visualize the stimulating influence of the DBS electrode in the target location before permanent implantation. Third, provide a common visualization platform to simultaneously analyze the anatomical (MRI/CT/3D brain atlas), neurophysiological (MER), and electrical (DBS VTA) data pertinent to the surgery.

In general, the MRI/CT scans with the stereotactic fiducial makers necessary for a human DBS procedure are acquired on the day of the surgery. Therefore, we

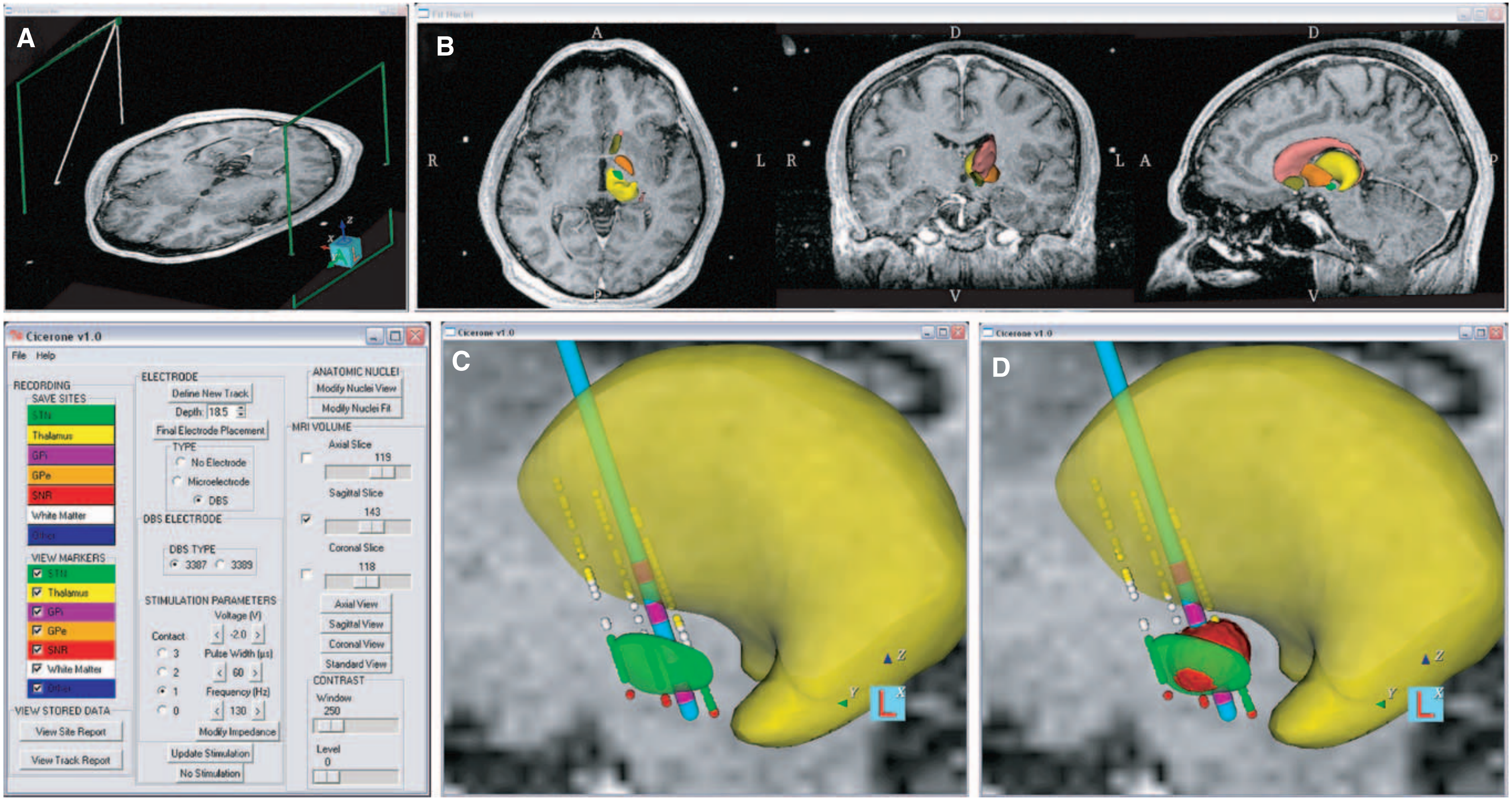


Fig. 1. Human Cicerone graphical user interface. (A) The green localizer box is manipulated to coincide with the stereotactic frame fiducial markers in the MRI. (B) A 3D brain atlas is customized to the subject's MRI with interactive scaling and translation. (C) Microelectrode recording data (*yellow dots* thalamus; *white dots* white matter; *green dots* STN; *red dots* SNr) and the DBS electrode position (*blue shaft with pink contacts*) can be viewed in stereotactic space with the MRI and anatomical nuclei (*yellow volume* thalamus; *green volume* STN). (D) Theoretical predictions of the volume of tissue that would be activated by DBS (*red volume*) can be visualized with any electrode position/trajectory and a range of stimulation parameter settings

developed our human Cicerone system to directly read in and interact with DICOM imaging data via a simple user interface; thereby decreasing the time needed to set up the system. When the user starts the program, they are prompted to enter any necessary patient/study identification data. Next, they navigate to the appropriate directory and load the patient's DICOM imaging data. A fundamental requirement of any stereotactic neurosurgical navigation system is the definition of a common coordinate system. In turn, the user must position a virtual replica of the frame fiducial system within the context of the MRI; thereby defining the stereotactic coordinate system relative to the imaging data (Fig. 1A). Version 1.0 of Cicerone has been designed to work with the Leksell stereotactic frame (Elekta Corp., Stockholm, Sweden). Following definition of the stereotactic frame coordinate system in the MRI, the user is prompted to select the right or left side of the brain for analysis. The user then orients the MRI along the midline using coronal and axial views, and defines the anterior commissure (AC) and posterior commissure (PC) in the image. The next step in the process consists of scaling and positioning 3D anatomical representations of nuclei of interest (e.g. subthalamic nucleus, globus pallidus, thalamus, etc.) (Fig. 1B). The anatomical nuclei are originally positioned within the context of the MRI based on the definition of the AC and PC. However, the user has the option to translate and/or scale the anatomical nuclei along the anterior/posterior, dorsal/ventral, and medial/lateral axes to enable the most accurate match possible with the MRI (Fig. 1B).

Once the Cicerone anatomical model has been defined relative to the MRI and stereotactic coordinate system, a preliminary target location and trajectory for the DBS electrode can be defined. This information can be used in conjunction with additional neurosurgical navigation systems and the stereotactic frame system to define the mechanical parameters of the frame apparatus (e.g. arc angle, collar angle, etc.). After a burr hole has been placed, the microdrive attached to the frame, and a cannula inserted along the initial trajectory to a specified depth above the target (15 mm at our institution), Cicerone can be used to visualize and record MER data (Fig. 1C). The user has the opportunity to identify each encountered cell as belonging to various anatomical nuclei and notes can be entered describing various electrophysiological characteristics (somatotopy, firing properties, background activity, etc.). The microelectrode recording (or stimulation) locations are displayed as small spheres and color-coded according to their user defined characteristics (Fig. 1C). The user can pan/zoom/rotate the view, adjust the display properties of the 3D brain atlas, and scroll through the MRI in three orthogonal planes. The recording markers and brain atlas can also be viewed in 2D, one slice at a time, which is sometimes preferable to a 3D view.

The fundamental advance of Cicerone over previous neurosurgical navigation software systems is the ability to predict the volume of tissue activated (VTA) by DBS for a given electrode position and stimulation parameter setting (Fig. 1D). This offers a great potential benefit to clinicians and researchers, enabling them to anticipate stimulation effects before the actual electrode implantation. The user can plan the electrode trajectory to achieve the desired interaction between the VTA, MER data, and 3D neuroanatomy (Fig. 1D). The computational details of generating VTA predictions are presented in our previous publications [4–6, 20]. Briefly, Cicerone employs pre-compiled solutions of the response of multi-compartment cable models of myelinated axons to electric fields generated by finite element models of DBS electrodes. The theoretical VTA predictions used in Cicerone explicitly account for the effects of electrode capacitance, electrode impedance, and the stimulation parameter settings (contact, voltage, pulse width, frequency) [4–6] (Fig. 1D).

Simultaneous interactive visualization of the anatomical, neurophysiological, and electrical data pertinent to the DBS surgery allows definition of an optimal placement for the permanent DBS electrode. In turn, the stereotactic coordinates of the Cicerone-derived optimal placement can be applied to the surgical frame and the DBS electrode can be implanted. Once the user has finished their data entry and analysis, the stereotactic coordinate system transfer functions, brain atlas scaling/positioning, MER data, and DBS electrode placement are saved to a text file that can be re-imported into the program at a later time or stored to a central database.

## Monkey Cicerone

The laboratory of Jerrold Vitek pioneered a parkinsonian non-human primate model of DBS that represents a powerful tool for experimental investigation on the therapeutic mechanisms of DBS [8, 14]. However, neurosurgical navigation systems customized for non-human primates are effectively non-existent. Therefore, we developed a monkey version of Cicerone (Fig. 2). It provides the same general features as the human version; however, differences in the stereotactic frame systems

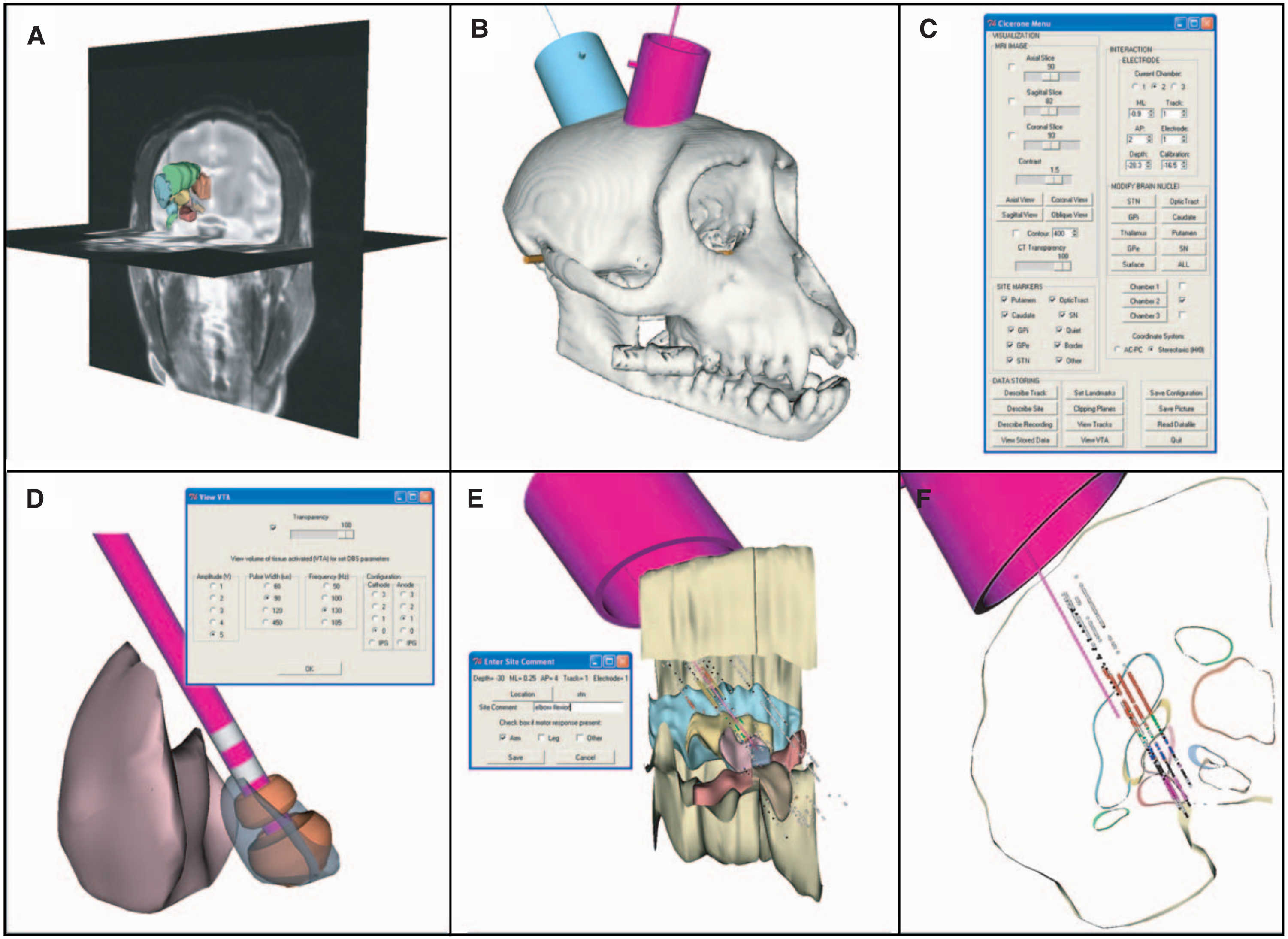


Fig. 2. Monkey Cicerone graphical user interface. (A) A 3D brain atlas is customized to the subject's MRI either by warping or linear scaling. (B) The contour of the skull is extracted from the CT data and co-registered with the MRI and 3D atlas. Electrode chambers are interactively positioned in the stereotactic coordinate system, defined by the ear bars and orbital bars. (C) Cicerone's main menu provides functions for image and data manipulation. (D) Orange ellipsoids inside the STN represent theoretical volume of tissue activated for the given DBS electrode position and stimulation parameters. (E) The user can enter information about each microelectrode recording site. The site markers are rendered in 3D with respect to the surrounding neuroanatomy. (F) Recording data and neuroanatomy can also be visualized in 2D, slice by slice

and surgical procedures require several differences in the software set-up. In monkey stereotactic neurosurgery, it is common to use a head frame and an atlas referenced to the orbitomeatal plane. This plane is defined by the interaural line (line between tips of the earbars) and the inferior orbital ridges. The origin is defined as the midpoint of the interaural line and the orbitomeatal plane (Frankfurt zero). For use in primate research, a CT is needed to visualize the skull and the external landmarks (ear canals and orbital ridges) so that the stereotactic head frame can be registered with the internal brain structures. The MRI is used to customize the 3D brain atlas and to locate internal landmarks on the CT. The MRI and CT are co-registered in Analyze 6.0 (AnalyzeDirect, Lenexa, KS) and imported into Cicerone as VTK volume files. Using the skull rendering extracted as a contour from the CT data, the user can position ear bars and orbital ridge bars to define the orbitomeatal plane (Fig. 2B). Cicerone enables the user to switch from the 'AC-PC coordinate system' to the 'stereotactic coordinate system' (i.e. orbitomeatal plane). When moving to the 'stereotactic coordinate system', rotation around mediolateral axis is performed so that the orbitomeatal plane is horizontal and the origin is shifted to Frankfurt zero.

The 3D brain atlas for non-human primates used in Cicerone was created from the University of Washington digital atlas of the longtailed macaque (*Macaca fascicularis*) brain [18] (Fig. 2A). A subject specific 3D brain atlas is constructed by warping 2D digitized atlas templates to the corresponding MRI slices using Edgewarp [1, 19]. Edgewarp applies a nonlinear warping function to atlas templates based on manual landmark selection. The warped atlas slices are converted into 3D volumes using the graphical modeling program Rhinoceros v 3.0 (McNeal & Associates, Seattle, WA). The customized 3D atlas is imported into Cicerone based on its registration with the MRI (Fig. 2A). Cicerone provides tools to interactively position up to three recording chambers on the animal's skull (Fig. 2B). This makes it possible to ensure, prior to surgery that the electrodes can reach the desired target areas and that the chambers and electrodes will not interfere with each other once placed on the skull. The user can also evaluate several chamber shapes to find the one that best fits the skull contour in a chosen location. The chamber placement coordinates provided by Cicerone can be applied directly to the stereotactic head frame. Cicerone's algorithm for coordinate calculation is designed for use with Kopf frame (model 1430 and electrode manipulator model 1460; David Kopf Instruments, Tujunga, CA). After the chamber placement surgery, it is advisable to perform another CT scan to verify the chamber position and angle on the skull.

During neurophysiologic data recording, the monkey and human versions of Cicerone are effectively the same. The user can interactively view the electrode position within the 3D anatomical environment by entering microdrive coordinates into Cicerone (Fig. 2C), MER data can be displayed (Fig. 2E and F), and DBS electrode positions can be evaluated with VTA predictions (Fig. 2D). One difference is the DBS electrode design used in the monkey. Our experimental monkey DBS electrodes are approximately one half the size of human DBS electrodes [8, 14]. In turn, the monkey Cicerone system has been customized to account for VTAs generated by monkey DBS electrodes (Fig. 2D). And similar to human Cicerone, the stereotactic coordinate system transfer functions, brain atlas scaling/positioning, MER data, and DBS electrode placement data are saved to a text file that can be re-imported into the program at a later time or stored to a central database.

## Conclusions

The Cicerone software system represents the first neurosurgical navigation system to integrate electrically accurate predictions of neurostimulation-generated by DBS electrodes. In addition, it allows the neurosurgeon to simultaneously visualize the anatomical (MRI/CT/3D brain atlas), neurophysiological (MER), and electrical (DBS VTA) data pertinent to the implantation of DBS electrodes. Therefore, pre/intra-operative optimization of the stereotactic trajectory and placement of the DBS electrode can be performed with results derived from theoretical characterization of the stimulating effects of DBS and patient-specific characterization of the brain region targeted for implantation. Further, Cicerone provides a platform for integrated analysis of the interaction between the neuroanatomy, neurophysiology, neurostimulation, and behavioral outcomes of DBS.

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## Conflict of interest statement

CRB and CCM are shareholders in IntElect Medical Inc., license holder for the neurostimulation prediction, optimization, and visualization intellectual property utilized in Cicerone.

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Correspondence: Cameron C. McIntyre, Department of Biomedical Engineering, Cleveland Clinic Foundation, 9500 Euclid Ave. ND20, Cleveland, OH 44195, USA. e-mail: mcintyc@ccf.org